Our ref: KON-1870 Client's ref: P6388-001-0000 (US)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re Application of: Eiichi UEDA, et al : Art Unit: 1618

Appln. No.: 10/824,095 : Examiner: M.J. Perreira

Filed: April 13, 2004 :

For: LIPOSOME-CONTAINING RADIOGRAPHIC CONTRAST MEDIUM AND PREPARATION METHOD THEREOF :

CONFIRMATION #6153

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DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

S i r:

I, Akihisa NAKAJIMA, hereby declare and say as follows:

1. I am one of the named Inventors in this Application.

2. I graduated from Osaka University in March of 1987 with a Masters Degree in Synthetic Chemistry. Since April of 1987, I have been employed by Konica Corporation, the Assignee of the above-identified

Application and have specifically been engaged in the research and development of photographic material supports.

3. I am aware that the Examiner has rejected the claims in this Application based on Otake (US 2004/0099976) or Castor (US 5,554,382) in view of Sachse, et al (*Invest Radiol. 1997.32.44-50)* and Mackaness (US 4,192,859) or Klaveness (US5,676,928). I am also aware that the Examiner has stated that neither Otake nor Castor disclose the inclusion of an iodine compound in the preparation of a liposome; or the inclusion of a water soluble amine compound in the preparation of a liposome. I am of the opinion that the preparation of a liposome including a water soluble non-ionic iodine compound by the use of supercritical carbon dioxide shows surprising and unexpected superior results in the weight percentage of the iodine compound that is included in the vesicle based on the total iodine compound compared to conventional practices and, especially, the teachings of, for example, Mackaness.

4. In order to demonstrate the surprising and unexpected results obtained by the present Invention, tests have been performed and the results of those tests are reported herein. These tests were conducted by me or under my direct supervision and control.

5. A first encapsulated substance, labeled Sample A, was prepared following Example 1 of Mackaness as taught in column 4, line 59 to column 5, line 3. The weight percent of the amount of iodine compound (the contrast agent) contained within the vesicle is reported in Table 4 as attached hereto.

6. A second encapsulated substance, labeled Sample B, was prepared in the same way as Sample A, except that iodine compound was replaced with L-ascorbyl phosphate. This phosphate is a pharmacologically active substance as taught by Otake, see paragraph 32 of Otake. Thus, a liposome was formed using the process of Mackaness but with a pharmacologically active ingredient. The weight percent of the phosphate in the vesicle is reported in Table 4.

7. A third encapsulated substance, labeled Sample C, was prepared following Example 1 of Otake as taught on page 4, paragraph 68. L-ascorbyl phosphate was injected into the pressure apparatus before the lipsosome was formed. The weight percent of the phosphate contained in the vesicle is reported in Table 4.

8. A fourth encapsulated substance labeled Sample D, was prepared in the same way as Sample C, except that the iodine compound of Mackaness, as contained in the 7 ml of neutral buffered solution, was injected into the pressure apparatus before the liposome was formed. The weight percent of the iodine compound contained in the vesicle are reported in Table 4 as attached hereto.

9. A fifth encapsulated substance labeled Sample E, was prepared in an identical manner to Sample D, above, except that 20 ml of ethanol was included with the iodine compound, as contained in 7 ml of neutral buffer solution, when injected into the pressure vessel prior to formation of the vesicles. The amount of the water soluble iodine compound contained in

the vesicles is reported in Table 4, attached hereto.

10. The determination of the amount of compound contained in the vesicle was determined in the same manner as disclosed in the Application, see page 43, line 17.

11. As can be seen in Table 4, the amount of pharmacologically active compound in the vesicle in Sample B was greater than the amount of iodine in the vesicle of sample A by a factor of 12. Thus, I would expect the proportion of iodine in the vesicle mode by Otake's process to be 1.25 based on Sample C (i.e.15 ÷ 12). I would also expect that the proportion of iodine in Otake's process to be 1.25 when comparing the difference between Samples B and C. Sample C is 2.5 times better than Sample B. Thus, I would expect the iodine proportion for Sample D to be 1.25 (2.5 x 0.5). It is surprising and unexpected that the amount of iodine in Sample D is 34 times greater than Sample A. It is also surprising that Sample E is on the order of 40 times better than Sample A.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 USC 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Akihisa Nakajima
Akihisa NAKAJIMA

Dated: This 12th day of March, 2008.

DCL/mr

Attached: Table 4

Table 4

Sample	method of preparing a liposome	organic solvent	substance to be encapsulated	propotion (weight percentage of compound included in vesicles based on total compound)	Remarks
A	the Example 1 of Machaness	chloroform	N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-1-oxopropyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide	0.5	Comparative
B	the Example 1 of Machaness	chloroform	magnesium L-ascorbyl phosphate	6	Comparative
C	the Example 1 of Otake	none	magnesium L-ascorbyl phosphate	15	Comparative
D	the Example 1 of Otake	none	N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-1-oxopropyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide	17	Inventive
E	the Example 1 of Otake	ethanol	N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-1-oxopropyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide	20	Inventive